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SIDNEY SOBIN AND HAYDEN C. NICHOLSON

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AN ANALYSIS OF THE FACTORS INVOLVED IN THE VARYING EFFECTS OF CARBON DIOXIDE UPON RESPIRATORY RATE¹

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An increase in the carbon dioxide of the inspired air most commonly produces a distinct increase in the depth of breathing with little change in rate. A distinct slowing or a marked acceleration may, however, occur. In a single series of experiments upon dogs with intact vagi and with the same type (morphine urethane) and approximately the same depth of anesthesia, we have found a 12 per cent to 14 per cent carbon dioxide mixture to cause changes in respiratory rate varying from an 85 per cent slowing to a 204 per cent acceleration. If the respiratory effect of carbon dioxide were dependent upon the action of the gas upon one mechanism alone, one would certainly expect a greater degree of constancy of effect than is observed. However, when one considers the fact that carbon dioxide stimulates the respiratory center, augments the discharge of peripheral chemoceptors and depresses reflex activity in general including vagal respiratory reflexes (Gesell and Moyer, 1935) it is not surprising that the resultant of these various effects is not constant. The picture is further complicated by the fact that the resultant respiratory effect of any procedure need not represent simply the algebraic sum of the effects upon the various individual structures involved. Thus, Gesell, Steffensen and Brookhart (1937) found that combined chemoceptor stimulation and vagal stimulation produced marked acceleration of respiration, while the former alone produced only a mild increase in respiratory rate, and the latter an actual slowing.

Since an important part of the central respiratory mechanism is apparently located very superficially in the floor of the fourth ventricle in the region of the calamus scriptorius (Nicholson, 1936) we felt that some information regarding the mechanism of CO₂ action might be obtained by studying the effects of irrigation of this region with Locke's solution equili-

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brated with CO_2 at various tensions. In our first experiments the Locke's solution at body temperature was equilibrated with 100 per cent CO_2 at atmospheric pressure or a mixture of 79 per cent CO_2 and 21 per cent O_2 . In contrast to the usual lack of marked change in rate from intrapulmonary administration, CO_2 administered in this way ordinarily caused a decided slowing of respiration. Figure 1 A is a typical example. Occasionally a slight acceleration was observed, but this was the exception and not the rule. In subsequent experiments the effect of varying the tension of carbon dioxide in the irrigating fluid was studied. In figure 1 C, 15 per cent CO_2 decreased the respiratory rate from 19 to 15 per minute (21 per cent) while in 1 D 79 per cent carbon dioxide in the same animal decreased the rate from 20 to 13.5 per minute (32 per cent). Figures 1 E and 1 F are from one of the rare experiments in which medullary

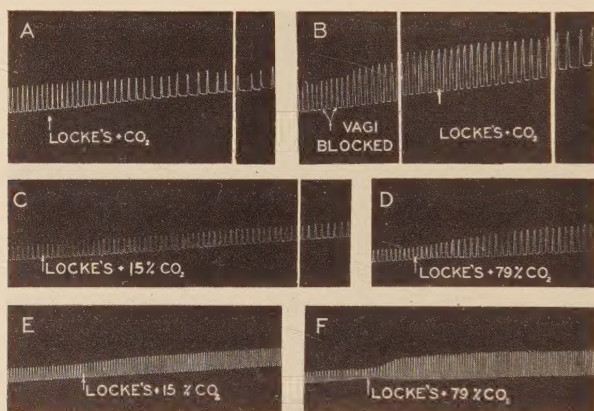


Fig. 1. Respiratory records in this and subsequent illustrations are spirometer tracings, upstroke representing inspiration.

irrigation with carbon dioxide increased the respiratory rate. In 1 E, 15 per cent carbon dioxide increased the respiratory rate from 28 to 34 per minute (21 per cent) while in 1 F, 79 per cent carbon dioxide increased the rate from 21 to 27 (29 per cent). It is evident then that this predominant tendency of carbon dioxide when applied to the floor of the fourth ventricle to slow respiration is relatively independent of the tension of the gas, a variation in tension varying the magnitude, but not the direction of the change.

Since the nucleus of the fasciculus solitarius lies near the surface of the brain stem in the region irrigated and since it has been shown that vagal reflexes may be abolished by cooling this region (Nicholson and Brezin, 1937) or applying cocaine to it (Nicholson and Sobin, 1938), this slowing of respiration by carbon dioxide might be purely the result of depression

of vagal reflexes. This possibility is rendered unlikely by the character of the slowing, which is to a considerable extent due to an increase in the duration of the expiratory pause while the slowing of respiration from vagotomy is due largely to an increase in amplitude and a decrease in the speed of inspiration. Furthermore, irrigation of the floor of the fourth ventricle with carbonated Locke's solution causes equal respiratory slowing after vagotomy. Figure 1 A shows a fairly typical response to irrigation with 100 per cent carbon dioxide. The respiratory rate decreased from 18 to 10 per minute, or 44 per cent. Vagotomy (fig. 1 B) slowed the rate from 19 to 14 per minute (26 per cent). Reëxposure of the calamus region to the same carbon dioxide solution now slowed the rate from 14 to 8 per minute, again a reduction of 44 per cent. This of course does not

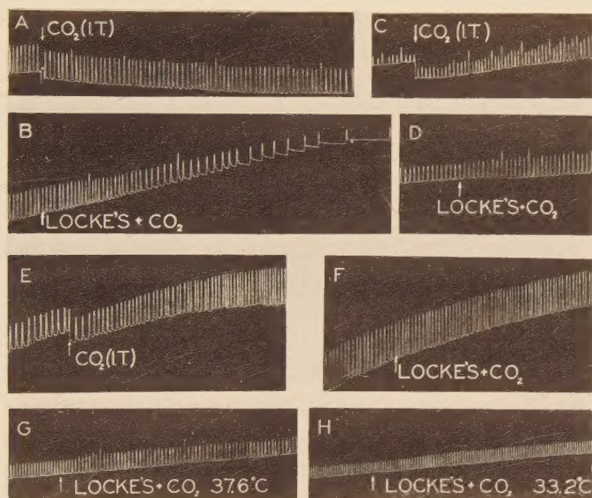


Fig. 2

mean that in the intact animal depression of vagal reflexes may not be an important factor in hypercapnic slowing. It may mean simply that following vagotomy other reflexes, also of course susceptible to hypercapnic depression, are now dominant.

Our next procedure was to compare the effects of intratracheal administration of CO_2 (12 to 14 per cent) with the effects of irrigation of carbonated Locke's solution in the same animal. When intratracheal administration of CO_2 decreased the respiratory rate, irrigation decreased the rate to a much greater extent. This difference is well shown in figures 2 A and B. In those cases in which intratracheal carbon dioxide caused a slight or moderate acceleration the usual effect of irrigation was a slight slowing or no change in rate. In figure 2 C intratracheal carbon dioxide

increased the respiratory rate from 15.5 to 17 per minute, a 16 per cent increase, while irrigation with Locke's solution plus carbon dioxide (2 D) failed to alter the respiratory rate. In those cases in which intratracheal carbon dioxide caused a very marked acceleration of respiration, irrigation might cause a slight acceleration. In figure 2 E, intratracheal carbon dioxide increased the respiratory rate from 11.2 to 23 per minute, 104 per cent, while in 2 F from the same animal irrigation increased the rate from 19.6 to 25 per minute, a 27 per cent increase. In a few experiments the effect of administration of carbon dioxide simultaneously by the two methods was determined. In some cases irrigation was initiated during the course of an intratracheal administration. In other cases the two procedures were carried out in the reverse order. The combined effect of the two was invariably a slowing of respiration, usually considerably more marked than one would expect from addition of the two individual effects.

From the above results it seems evident either that carbon dioxide centrally applied compared with intratracheal administration exerts a disproportionate effect on the same factors of the central integrative mechanism or that new types of action are open to irrigation not available to ordinary intratracheal administration. The former possibility seems the more likely though a combination of the two should be considered. In previous work we have demonstrated the presence of a mechanism in the region of the calamus scriptorius which is apparently responsible for interrupting inspiration and bringing about expiration. This mechanism seems to be readily depressed by cooling (Nicholson, 1936) and by cocaine (Nicholson and Sobin, 1938) and is apparently stimulated by the local application of nicotine (Nicholson and Sobin, 1938). In view of these results it seems not unlikely that the *marked* decrease in respiratory rate resulting from irrigation of the floor of the fourth ventricle with solutions containing carbon dioxide may be due in part at least to a stimulation of this expiratory mechanism by the carbon dioxide. If this is the case, one would expect that depression of this expiratory mechanism by cooling should diminish or abolish the slowing effect of carbon dioxide and we have found this to occur. In figure 2 G, irrigation of the floor of the fourth ventricle with carbonated Locke's solution decreased the respiratory rate from 30.5 to 23 per minute (24 per cent). In this experiment the Locke's solution, as was ordinarily the case, was at body temperature. The temperature of the Locke's solution was then lowered to 33.2°C and although equilibrated with the same tension of carbon dioxide (79 per cent) now had no effect on respiratory rate (fig. 2H). (It is of interest in this connection that Nicholson and Brezin (1937) observed a marked exaggeration of the accelerating effect of intratracheal carbon dioxide as a result of moderate cooling of the calamus scriptorius.)

Time relations of the respiratory cycle. More direct information as

to the mode of action of CO_2 is afforded by examination of various phases of the respiratory cycle. While in the preceding sections, attention was drawn to the differences between the effects of CO_2 administered intra-tracheally and by irrigation, the phase relationships in the two cases are essentially of the same nature, and thus to a great extent independent of the mode of carbon dioxide administration. Respiration has been long divided into two phases, inspiration and expiration, the latter phase subdivided into a stage of movement of air, and one when the chest is in the position of expiratory arrest. Gesell (1936), in studying potentials of inspiratory and expiratory muscles, drew attention to the fact that expiration is in part determined by persistence of inspiratory discharges, and from further evidence to be summarized later, we have found it convenient to consider as one period inspiration plus the first phase of expiration. This we have referred to as the period of *inspiratory stress*, as opposed to the expiratory pause. Graphically it represents the period

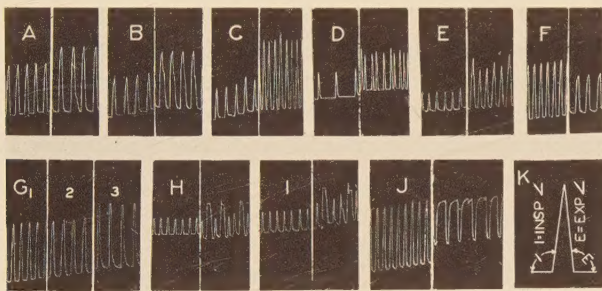


Fig. 3

between the departure of the curve from the base line and its return. Changes in inspiratory stress can be brought about by either changes in the duration of the inspiratory movement, in the length of time inspiration is maintained, or in the time that air is leaving the lungs, or any combination of these.

In all cases where the response to increased alveolar carbon dioxide or irrigation of carbon dioxide over the floor of the fourth ventricle manifested itself by a decrease in the respiratory rate, the period of inspiratory stress increased. The expiratory pause, however, was variable in this type of response. In less than half of the total observations did it increase. In figure 3 A, a respiratory slowing of 15 per cent occurred; inspiratory stress increased by 74 per cent and the expiratory pause decreased 38 per cent.

When hypercapnia produced an increased respiratory rate, the expiratory pause invariably shortened. Changes in inspiratory stress were in part determined by the degree of hyperpnea produced. When the acceleration was marked, the decrease in expiratory pause was aided by a

decrease in inspiratory stress, both contributing to a more rapid respiratory cycle. On the basis of the total observations of an increased respiratory rate, 50 per cent showed an increase in inspiratory stress, 20 per cent exhibited little change, and 30 per cent decreased. These various types of response are illustrated in figures 3 B, C and D. In figure 3 B there was an increase in respiratory rate of 21 per cent due entirely to a 66 per cent decrease in the duration of the expiratory pause, the period of inspiratory stress actually increasing 55 per cent. In 3 C the respiratory rate increased 100 per cent with no change in the duration of the period of inspiratory stress, while in 3 D there was an acceleration of 181 per cent to which both the expiratory pause and the period of inspiratory stress contributed, the former by a decrease of 61 per cent and the latter by a decrease of 39 per cent.

It is of interest that in many cases where CO_2 produces little or no change in the total respiratory rate, marked changes in phase relationships may occur. In figure 3 E, CO_2 produced no change in rate, but while in the normal cycle inspiratory stress occupied 30 per cent of the cycle, during the hypercapnic state it occupied 72 per cent of the cycle. Thus a 138 per cent increase in inspiratory stress counterbalanced a 68 per cent decrease in expiratory pause.

These observations leave no doubt as to the inadequacy of the statement of Hammouda and Wilson (1932) that the sum of the duration of the first two phases of respiration is relatively constant under various experimental conditions, variations in the respiratory rate resulting almost entirely from variations in the duration of the expiratory pause.

Form of the respiratory cycle. In 1935 Gesell and Moyer introduced the term "chemical vagotomy" for the relatively slow breathing produced by depression of the vagal reflex under exposure to CO_2 , this being a specific application of the depressant effects of CO_2 on spinal cord reflexes (Glazer, 1929). Carbon dioxide administration is not infrequently accompanied by a marked slowing of the speed with which inspiration proceeds. This may readily be detected by measuring the angle which the inspiratory tracing makes with the base line, angle I in figure 3 K. In figure 3 F carbon dioxide irrigation decreased the respiratory rate from 21 to 13.5 per minute and increased this inspiratory angle from 93° to 94.7° . Examination of this record further shows that this slowing of inspiration becomes more marked as inspiration approaches its peak. Nicholson and Brezin (1937) pointed out that the most characteristic effect of vagotomy on breathing is the increase in duration of the inspiratory phase, and Gesell, Steffensen and Brookhart (1937) demonstrated an *acceleration of inspiration* with electrical stimulation of the vagi. Thus the decrease in the speed of inspiration by CO_2 can be interpreted as vagal depression.

However, this slowing of inspiration in hypercapnia is not the most

common finding. More frequently carbon dioxide has just the opposite effect; namely, a quickening of inspiration. This effect is well illustrated in figure 3 G where the normal respiratory cycle (G_1), the response to a medullary irrigation of carbon dioxide (G_2), and the additive effects of an intratracheal carbon dioxide administration (G_3) have in the order given, inspiratory angles of 92.1° , 91.6° and 90° . This increased speed of inspiration might conceivably be due to either of two causes: 1, a central blocking of the restraining effect which afferent impulses may have on inspiration, or 2, a stimulation of an inspiratory mechanism. Barcroft (1934) believes that the gasp, which consists of an abrupt swift inspiration terminating suddenly in an abrupt swift expiration, represents the fundamental unit of respiration and that it appears upon complete removal of all the factors inhibiting respiration. If this is the case, blocking of inhibiting impulses might be involved in this acceleration of inspiration by carbon dioxide. Barcroft emphasizes the depressant action of carbon dioxide upon nervous processes stating that, "It is much easier to conceive of carbon dioxide as paralyzing a nervous process than as stimulating it," and again, "that carbon dioxide acted like making suitable cuts through the medulla." However, we are inclined strongly to the view that the increased speed of inspiration frequently seen in hypercapnia is the result of inspiratory stimulation. In the first place there is little or no evidence in favor of the view and considerable fairly direct evidence against the view that removal of afferent impulses favors gasping respiration or an increase in the speed of inspiration. In the second place, in the experiments of Samaan and Stella (1935) upon the discharge of carotid gland receptors we have direct evidence of stimulation of a nervous process by carbon dioxide. Finally, we are forced to the view that carbon dioxide is stimulating inspiratory activity by a consideration of the effects of CO_2 on the speed of expiration.

Expiration in the hypercapnic state, when compared with the normal is markedly slowed. Thus in figure 3 G, the normal expiratory angle is 92.5° ; irrigation with CO_2 increased the angle to 95° while addition of intratracheal carbon dioxide further increased it to 97° . It will be recalled that the total period of inspiratory stress invariably increased when CO_2 caused a slowing of respiration and increased in a considerable number of the cases when CO_2 caused an increase in respiratory rate. *The most important factor involved in increasing the duration of the period of inspiratory stress apparently is this decrease in the speed of expiration.* This marked slowing of expiration can only be explained by a persistence of activity in the inspiratory muscles, further evidence we believe of inspiratory stimulation by CO_2 . That activity in inspiratory muscles may disappear only gradually as expiration proceeds has been amply demonstrated by Gesell (1936) as he says in the discussion of electromyograms, "final deflation was only accomplished as inspiratory potentials faded from

the record." In addition, recent work of Gesell and White (1938) has shown that in cyanide hyperpnea there is a long after-discharge of inspiratory muscles, and with it, a marked slowing of mechanical expiratory effort.

Apneustic respiration. This type of respiration, breathing characterized by a tendency to hold the breath in the inspiratory position, may be seen in hypercapnia. Although apneustic breathing was observed as early as 1880 (Marckwald and Kronecker) Lumsden (1923) reinvestigated the problem by means of sectioning the brain stem, and arrived at his well known series of phylogenetic centers stretching from the calamus to the upper pons. Subsequently, apneustic breathing has been produced in a variety of ways—by section of the rubrospinal tracts plus section of the vagi (Henderson and Sweet, 1929), by local cooling of the floor of the fourth ventricle (Nicholson, 1936), by hydrocyanic acid gas (Taylor, 1930), by carbon dioxide (Barcroft and Margaria, 1932) and by cocaineization of the floor of the fourth ventricle (Nicholson and Sobin, 1938).

Figures 3 G, H and I illustrate various types and degrees of apneustic breathing seen with carbon dioxide administration. Figure 3 G₃ as contrasted with figure 3 G₁ shows a slight but definite pause at the height of inspiration (as well as a more abrupt inspiratory movement and greatly delayed expiratory movement). In figure 3 H the carbon dioxide was administered by irrigation of the floor of the fourth ventricle while in 3 I it was administered intratracheally. A definitely prolonged inspiratory pause is in evidence in both of these records, as well as the other changes mentioned above.

From purely theoretical considerations, it is apparent that maintained inspiration can result from either 1, the inability of some normally occurring inhibitory process to interrupt inspiration, or 2, intense and prolonged stimulation of an inspiratory mechanism. Of all the methods used to produce apneusis, central cooling is perhaps the one that most certainly produces depression with no concomitant stimulation. In figure 3 J we see an example of apneustic respiration resulting from local cooling of the surface of the brain stem. When we examine this record we see that inspiration is actually slower than in the normal record, the tracing sloping off more and more as the ascent continues, presenting a distinctly rounded appearance as it approaches its peak. The inspiratory pause is then maintained for a considerable length of time finally being terminated by an abrupt, very rapid, expiration. The apneustic curves of hypercapnia (fig. 3 G, H, I) present almost the exact opposite sort of picture, inspiration proceeding more rapidly than normal and expiration more slowly. The only common attribute of cooling and CO₂ curves is the presence of maintained inspiration. Yet it was the production of apneuses by CO₂ that led Barcroft to state that "carbon dioxide acted like making suitable cuts

through the medulla," and doubtless confirmed his belief in the predominantly depressant action of CO_2 . The records of Barcroft and Margaria (1932) also show this increased speed of inspiration and Barcroft (1934) speaks of apneusis as being characterized by increased speed of inspiration; Taylor's records of apneusis produced by cyanide show both types of apneusis.

Any mechanism that slowly and gradually builds up to a maximum and then by virtue of continued supply of energy and lack of a restraining influence continues to discharge, will produce the type of picture presented by cold apneusis. But conversely, where energy input is very abrupt and rapid and continues at a high level, a sudden inspiration, and very long delayed expiration will result. Expressed in terms of C. E. S. and C. I. S. these illustrations fit into the scheme laid down by Gesell and co-workers (1937). We have here, then, a method of evaluating the mode of action of various respiratory procedures. It is not conceivable that rapid inspiration, maintained inspiration and delayed expiration are all the results of different types of action when they are observed in one respiratory cycle. The close dependence of all the phases of the inspiratory stress period on the discharge of the inspiratory side of the respiratory mechanism is thus all the more apparent.

While at the present not desirous of entering the field of architectural organization of the respiratory center or centers, certain contradictions should be pointed out. Lumsden's and Barcroft's views as to the phylogenetic nature of the various centers (either as a group or as a single center with various degrees of inhibition) are based in the former case on the presence of apneustic respiration in chelonians and in the latter case, in part, on presence of "gasping" respiration in the hibernating marmot. Yet, Popoff and Romanovskaya (1930) were able to convert pneumotaxic to apneustic respiration in the frog by cocaineization of the medulla (see Nicholson and Sobin, 1938) and Marckwald (1888) produced apneusis in the sleeping marmot by simply cutting the vagi.

SUMMARY

Carbon dioxide administered intratracheally to anesthetized dogs commonly has little effect upon respiratory rate although either slowing or acceleration may occur.

Irrigation of the floor of the fourth ventricle with Locke's solution equilibrated with CO_2 may also alter respiratory rate in any direction though the usual effect is a slowing, sometimes extreme in degree. The direction of the change in rate is independent of the tension of the gas. The slowing is not prevented by vagotomy, but is diminished by cooling the floor of the fourth ventricle. Simultaneous administration of intratracheal carbon dioxide accentuates the slowing.

